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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/934,706	08/23/2001	Tetsuya Ishikawa	029650-103	9286

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EXAMINER	
MONDESI, ROBERT B	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/934,706	ISHIKAWA ET AL.	
	Examiner	Art Unit	
	Robert B Mondesi	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 15, 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☒ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Priority

The current application filed on August 23, 2001 claims priority to non – ptovisional application 09/507,691 filed on February 22, 2000, which in turn claims priority to foreign application, Japan 11-041913 filed on February 19, 1999 and foreign application, Japan 11-311364 filed on November 11, 1999. A certified translation of foreign documents Japan 11-041913 and Japan 11-311364 have not been provided.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Information Disclosure Statement

The IDS filed August 23, 2001 has been received and is signed and considered, a copy of the IDS is attached to the following document.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4, 6, 8 and 15, 18 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 2, 4, 6 and 8 the applicant makes reference to amino acid sequences that extent from Ala^{260}, Val^{262}, Val^{377}, Leu^{483}, Ala^{261}, Arg^{484}, Ala^{261} or Asp^{485} to variety of amino acids downstream from the initially mentioned amino acid. With the exception of claim 4, the applicant has not stated if these sequences are part of a particular peptide and as a consequence it is not clear or explained what the actual sequence that the applicant is referring to is supposed to be. **In claim 4** and in the specification the applicant makes reference to the amino acid sequence of the human fibronectin. It is known in the art that there are alternative splicings of the fibronectin glycoprotein. Manabe et al. and Kornblihtt et al. (cited in IDS filed August 23, 20021) disclose a complex pattern of fibronectin splicing at the mRNA level that allows for a variety of human fibronectin polypeptides with different structure and function. Since the applicant has not stated which splicing pattern of the human fibronectin glycoprotein is being referred to, amino acid sequences that simply draw homology to human fibronectin glycoprotein and do not disclose a specific amino acid sequence are considered to be indefinite. All claims will be prosecuted on the basis of the disclosed amino acid sequence of SEQ ID. NO: 1.

In claim 15 the phrase "inhibited competitively" is indefinite. The applicant has not defined in the specification what is meant by "competitive inhibition". The applicant

also has not defined what the fibronection glycoprotein is competing against in order to inhibit the binding activity of the collagen-binding physiologically active polypeptide.

In **claims 18 and 20**, the phrase "an agent for enabling" has not been defined by the applicant in the specification. It is not clear as to what the nature of the agent is, nor is it clear how the agent is enabling the topical retention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The polypeptide as claimed, has an amino acid sequence duplicative of that of the protein present in Manabe et al. or the cellular precursor thereof and possesses the biological and functional properties of the naturally occurring polypeptide human fibronectin and therefore does not constitute patentable subject matter absent recitation of "isolated or purified" in the preamble.

See *American Wood v. Fiber Disintegrating Co.*, 90 U. S. 566 (1974); *American Fruit Growers v. Brogdex Co.*, 283 U. S. 1 (1931); *Funk Brothers Seed Co. v. Kalo Inoculant*, 33 U. S. 127 (1948); and *Diamond v. Chakrabarty*, 206 USPQ 193 (1980).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5, 7 and 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Hashi et al. US Patent 5,302,701. Hashi et al. disclose a polypeptide construct comprising a peptide having collagen binding activity, like that of fibronectin, wherein the said peptide is connected with a spacer to a second peptide having physiological activity different from fibronectin activity (column 2, lines 23-44 and example 1) (**present claims 1 and 15**). With regards to protease-hydrolysis fragment of fibronectin, it is well known in the art that fibronectin can be enzamatically digested, to smaller fragments ranging from 28kDa to 75Kda (Engvall et al., US Patent 4,391,749, column 3 lines 17-24 and examples I-III), by a variety of proteases such as; trypsin (Mosher and Proctor) (**present claims 5 and 7**), chymotrypsin (Ehrismann et al.) (**present claims 3 and 7**), thrombin (Furie and Rifkin), plasmin (Jilek et al.) (**present claim 3**), elastase (McDonald and Kelly), chymase and cathapsin (Varieto et al.). **Claims 16-17** cite a collagen binding-physiologically active polypeptide constuct according to **claim 1** that is produced in bacteria or in a transformant containing a recombinant vector. These claims are in a product by process format absent factual evidence to the contrary, the product is not different from the prior art since the process steps do not contain indicia of production of a new product with new physical, chemical or biological properties and functions. Hashi et al disclose the polypeptide of these claims (column 2, lines 23-44) (**present claims 16-17**). Thus Hashi et al. teach all the

elements of **claims 1, 3, 5, 7 and 17-18** and these claims are anticipated under 35 USC 102(b).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hashi et al. US Patent 5,302,701 in view of Tuan et al. (cited in IDS filed August 23, 2003). Hashi et al. disclose a polypeptide construct comprising a peptide having collagen binding activity, like that of fibronectin, wherein the said peptide is connected with a spacer to a second peptide having physiological activity different from fibronectin activity. Hashi et al. also teach further that the amino acid sequence used as a spacer

may be appropriately selected depending on the purpose (**present claim 13**) . Hashi et al. do not explicitly teach that the second peptide is fused on the carboxyl terminal side of said first peptide is a cytokine that is a growth factor. Tuan et al. disclose a hybrid construct that comprises a spacer with a protolytic site, a first peptide with collagen binding activity and a second peptide that is a cytokine. Tuan et al. further disclose that the cytokine of the mentioned hybrid construct is a growth factor and is fused on the carboxyl side of the first peptide (materials and methods, figure 1) (**present claims 9-12**). Tuan et al. also disclose that the carboxyl end of the amino acid spacer used in their construct is a proteolytic site (Figure 1) (**present claim 14**). The Transforming Growth Factor beta (TGF-β) super family is a large group of cytokines that exert profound influences on the physiology of wound healing. Numerous animal studies have demonstrated the efficiency of exogenous (TGF-β) in promoting wound healing, the treatment of diabetic ulcers, and burns. However, clinical interest in the use of such cytokines as therapeutic agent has been hampered by the limited availability of such proteins. Genetic engineering and expression of such proteins in E. coli followed by purification and renaturation allows for a useful method for obtaining such cytokines. One of ordinary skill in the art would have combined Hashi et al. and Tuan et al. for the advantages a biological hybrid protein that could have been genetically engineered in order for ease of purification. A collagen-binding domain can be used to attach the hybrid product to the desired chromatography matrix, a proteolytic spacer could have been designed to release the desired cytokine. And since most proteases cleave the carboxyl terminal of the recognition sequence when the protease recognition sequence

is added on the amino terminal of the cytokine no excessive sequence is left on the amino terminal of the cytokine after the cleavage by the protease. As combined, Hashi et al. and Nishi et al. et al. demonstrate that one of ordinary skill in the art would have made and used the claimed invention prior to the time the claimed invention was made. Thus the claimed invention would have been prima facie- obvious at the time it was made.

Claims 1-8 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hashi et al. US Patent 5,302,701 further in view of Irani et al. US Patent 5,830,700. Hashi et al. disclose a polypepyide construct as explained above (**claims 1, 3, 5 and 7**). Hashi et al. further teach that fibronectin (FN) is a glycoprotein which is contained in the plasma and extarcellular matrix and has various functions and thus attempts have been made apply natural FN to drugs , eye drops and cosmetics (column 1) (**claim 18**). Hashi et al. do not expressly teach the amino acid sequence disclosed by SEQ ID NO:1 set forth in claims 2, 4, 6 and 8. Irani et al. disclose hybrid proteins having cross linking and tissue-binding activities useful in tissue sealant and wound healing formulations (see abstract and page 2). Irani et al. also disclose that the hybrid construct comprises a polypeptide, which has collagen binding activity, and consists of an internal amino acid sequence that is 99.4% similar to SEQ ID NO:1 (column 36, SEQ ID NO:2 , Ala^{291} to Trp^{630}). Non-recombinant fibrin based tissue adhesives and fibroblast growth factors have been known to have significant draw backs that include poor standardization, lack of quality control from batch to batch and the possibility of transmission of human immunodeficiency virus and other etiologic agents. Besides the previously mentioned

drawbacks, fibronectin and fibroblast growth factors purified from blood are only restrictedly supplied and are expensive. Under these circumstances an artificial polypeptide having cell adhesive activity and having fibroblast growth activity is extremely desirable. One of ordinary skill in the art would have combined Hashi et al. Irai et al. for the advantages of a collagen-binding polypeptide construct comprising a peptide having collagen binding activity, consisting of an internal amino acid sequence disclosed in SEQ ID NO:1, wherein the said peptide is connected with a spacer to a second peptide having physiological activity different from fibronectin activity. Such a construct is extremely desirable since the recombinant proteins expressed are isolated and purified using conventional methods and the production of such polypeptide can be extremely cost effective and efficient. There have been a variety chromatographic methods designed to take advantage of the collagen binding activity of fibronectin. A hybrid construct having fibronectin activity can be easily isolated and purified. Furthermore, if the mentioned hybrid construct is designed in a manner wherein the two peptides are separated by a cleavage site, than it is possible for the construct to be split in two segments for the advantageous of providing two different products. As combined, Hashi et al. Irai et al. demonstrate that one of ordinary skill in the art would have made and used the claimed invention prior to the time the claimed invention was made. Thus the claimed invention would have been prima facie- obvious at the time it was made.

Claims 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hashi et al. US Patent 5,302,701 as applied to **claim 1** above, and further in view of

Geistlich et al. US Patent 5,837,278. **Claims 19-20** are further limitations of **claim 1** that cite a biomaterial comprising a composite wherein the collagen-binding physiologically active polypeptide of **claim 1** is combined with collagen. Hashi et al. and do not disclose biomedical material comprising a composite wherein a collagen-binding physiologically active hybrid polypeptide is combined with collagen. Geistlich et al. disclose a biomaterial comprising collagen (claim 1 of patent 5,837,278). Collagen is useful as a biomaterial for use in tissue regeneration and wound repair. It has been shown that collagen is especially beneficial in guided tissue regeneration after such procedures as orafaciel and dental surgery. In such situations it is often important for bone regeneration to begin taking place immediately after the surgical procedure. One of ordinary skill in the art would have combined Hashi et al. Geistlich for the advantages of a biomaterial consisting of collagen and a collagen-binding polypeptide construct comprising a peptide having collagen binding activity wherein the said peptide is connected to a second peptide having physiological activity different from fibronectin activity. The incorporation of collagen with the hybrid polypeptide of the invention allows for an efficient wound healing biomaterial that could be used in procedures such as dental surgery wherein tissue repair and bone regeneration are of utmost importance. (**present claims 19-20**). As combined, Hashi et al. and Nishi et al. et al. demonstrate that one of ordinary skill in the art would have made and used the claimed invention prior to the time the claimed invention was made. Thus the claimed invention would have been prima facie- obvious at the time it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert B Mondesi whose telephone number is 703-305-4445. The examiner can normally be reached on 9am-5pm, Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

RBM

Robert B Mondesi
Patent Examiner
Group 1653
12-16-03

ROBERT A. WAX
PRIMARY EXAMINER